Claims

1. A proteasome inhibitor comprising, as an active ingredient, a carboxylic acid derivative represented by the formula (I) or a pharmaceutically acceptable salt thereof:

$$\begin{array}{c|c}
R^1 & & O & \\
R^2 & & M & N^2 & R^5 \\
P & & & R^4
\end{array}$$
(I)

<wherein m and n are the same or different and represent an</p> integer of 0 to 10; p represents 0 or 1; R1 represents a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alicyclic alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl or NR6R7 {wherein R⁶ represents a hydrogen atom, substituted or unsubstituted alkyl, or substituted or unsubstituted aralkyl, and R⁷ represents a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, CW1R8 (wherein R8 represents a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkylamino, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted substituted or unsubstituted aralkylamino, or aralkyl, substituted or unsubstituted aralkyloxy, and W represents an oxygen atom or a sulfur atom), or the formula:

$$R^9R^{10}N$$

(wherein R^9 represents a hydrogen atom, substituted or unsubstituted alkyl, or substituted or unsubstituted aralkyl; R^{10} represents a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, CW^2R^{8a} (wherein R^{8a} and W^2 have the same significances as the above R^8 and W^1 , respectively), substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, or $PW^3R^{12}_2$ (wherein R^{12} 's are the same or different and represent substituted or unsubstituted alkyl, or substituted or unsubstituted aryl; and W^3 has the same significance as the above W^1); or R^9 and R^{10} together represent the formula:

(wherein Y¹ represents substituted or unsubstituted alkylene or substituted or unsubstituted arylene); and R¹¹ represents a hydrogen atom, substituted or unsubstituted alkyl, or substitutedorunsubstitutedaralkyl)}; R² represents a hydrogen atom, COR¹³ (wherein R¹³ represents hydroxy, substituted or unsubstitutedalkoxy, substitutedorunsubstitutedalkenyloxy, substituted or unsubstituted aralkyloxy, substituted or unsubstituted aralkyloxy, substituted or unsubstituted alicyclic alkylalkoxy, substituted or unsubstituted aroylalkoxy, or NR¹⁴R¹⁵ (wherein R¹⁴ represents

a hydrogen atom, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl; and R15 represents unsubstituted alkyl, substituted or substituted aralkyl, unsubstituted substituted or unsubstituted alkoxycarbonylalkyl, amino, substituted or unsubstituted alkylamino, or substituted or unsubstituted arylamino; or R14 and R15 together with the adjacent N form a substituted or unsubstituted heterocyclic group)) or CH2OR3a (wherein R3a represents a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, substituted unsubstituted alkanoyl, substituted or unsubstituted aroyl, or SiR163 (wherein R16's are the same or different and represent substituted or unsubstituted alkyl, or substituted or unsubstituted aryl)); or R1 and R2 together represent the formula:

$$\begin{array}{c}
 & O \\
 & \downarrow \\$$

(wherein Y² represents substituted or unsubstituted alkylene);
X¹ represents a bond, substituted or unsubstituted alkylene,
substituted or unsubstituted alicyclic alkylene, substituted
or unsubstituted alkenylene, or substituted or unsubstituted
arylene; X² represents an oxygen atom, a sulfur atom or NR¹¹²
(wherein R¹² represents a hydrogen atom, substituted or

unsubstituted alkyl, or substituted or unsubstituted aralkyl); R³has the same significance as the above R³a; R⁴ represents hydroxy, mercapto, substituted or unsubstituted alkoxy, or substituted or unsubstituted alkylthio; or R³ and R⁴ together represent a bond; and R⁵ represents a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkenyl, or substituted or unsubstituted alkenyl.

- 2. The proteasome inhibitor according to claim 1, wherein \mathbb{R}^3 and \mathbb{R}^4 together represent a bond.
- 3. The carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to claim 1, wherein R^4 is hydroxy, or substituted or unsubstituted alkoxy; p is 1; R^1 is a hydrogen atom or NR^6R^7 (wherein each of R^6 and R^7 has the same significance as defined above), or R^1 and R^2 together are the formula:

$$\begin{array}{c}
O \\
HN \\
Y^2 \\
N \\
N \\
H
\end{array}$$
(R²)

(wherein Y^2 has the same significance as defined above); X^1 is substituted or unsubstituted alicyclic alkylene, or substituted or unsubstituted arylene; and X^2 is NR^{17} (wherein R^{17} has the same significance as defined above).

4. The carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to claim

- 1, wherein R^4 is mercapto, or substituted or unsubstituted alkylthio, or R^3 and R^4 together are a bond; X^2 is NR^{17} (wherein R^{17} has the same significance as defined above)[when m is 0; n and p are 1; R^2 is carboxy; R^3 and R^4 together are a bond; R^5 is sec-butyl; and X^1 is cyclopropylene or ethylene, R^1 is neither $NHC(=0)-C(CH_3)NH_2$, nor $NHC(=0)-C(CH_3)NHC(=0)O-C(CH_3)_3$].
- 5. The carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to claim 3, wherein R^1 is a hydrogen atom or NR^6R^7 (wherein each of R^6 and R^7 has the same significance as defined above).
- 6. The carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to claim 5, wherein R^1 is NR^6R^7 (wherein each of R^6 and R^7 has the same significance as defined above); X^1 is cyclopropylene or alkylene; and X^2 is NH.
- 7. The carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to claim 4, wherein R⁴ is mercapto, or substituted or unsubstituted alkylthio; R¹ is NR⁶R⁷ (wherein each of R⁶ and R⁷ has the same significance as defined above); and X¹ is cyclopropylene or alkylene.
- 8. The carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to claim 4, wherein R^3 and R^4 together are a bond.
 - 9. The carboxylic acid derivative or the

pharmaceutically acceptable salt thereof according to claim 8, wherein m is 0; n and p are 1; R¹ is NR⁶R⁷ (wherein each of R⁶ and R⁷ has the same significance as defined above); R² is COR^{13a} (wherein R^{13a} is alkylamino, aralkyloxy or aralkylamino); R⁵ is alkyl; X¹ is cyclopropylene, alkylene, or substituted or unsubstituted phenylene; and X² is NH.

10. A process for producing the carboxylic acid derivative according to claim 1, wherein R^3 and R^4 together represent a bond and X^2 is NR^{17} , characterized in that a carboxylic acid represented by the formula (II):

$$HO_2C$$
 R^5 (II)

(wherein R⁵ has the same significance as defined above) is reacted with an amine represented by the formula (III):

$$\begin{array}{c|c}
R^1 & & \\
 & & \\
R^2 & & \\
P & & \\
\end{array}$$

$$\begin{array}{c|c}
 & NH & \\
 & 17 & \\
 & R^{17} & \\
\end{array}$$
(III)

(wherein each of m, n, p, R^1 , R^2 , R^{17} and X^1 has the same significance as defined above).

- 11. The carboxylic acid according to claim 10, wherein R⁵ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted aralkyl, or a salt thereof.
- 12. The amine according to claim 10, wherein m is 0; n and p are 1; R^1 is NR^6R^7 (wherein each of R^6 and R^7 has the same significance as defined above); R^2 is COR^{13} (wherein R^{13}

has the same significance as defined above) or CH_2OR^{3a} (wherein R^{3a} has the same significance as defined above), or R^1 and R^2 together are the formula:

$$\begin{array}{c}
O \\
HN \\
/2 \\
Y^2 \\
N \\
H
\end{array}$$

$$\begin{array}{c}
(R^2) \\
(R^1) \\
N \\
H
\end{array}$$

(wherein Y^2 has the same significance as defined above); and X^1 is cyclopropylene, or a salt thereof.

- 13. The amine or the salt thereof according to claim 12, wherein R^1 is amino and R^{17} is a hydrogen atom.
- 14. The amine or the salt thereof according to claim 13, wherein \mathbb{R}^2 is carboxy.
- 15. A pharmaceutical composition comprising the amine or the salt thereof according to any one of claims 12 to 14 as an active ingredient.
- 16. A compound wherein the amine according to any one of claim 12 to 14 is protected with a protecting group, or a salt thereof.
- 17. A pharmaceutical composition comprising the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 as an active ingredient.
- 18. A proteasome inhibitor comprising the carboxylic acid derivative or the pharmaceutically acceptable salt thereof

according to any one of claims 3 to 9 as an active ingredient.

- 19. An antitumor agent comprising the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 as an active ingredient.
- 20. A pharmaceutical composition comprising the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 as an active ingredient, used for the treatment of the diseases curable by proteasome inhibition.
- 21. A use of the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 for the manufacture of a proteasome inhibitor.
- 22. A use of the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 for the manufacture of an antitumor agent.
- 23. A method to inhibit proteasome comprising a process in which an effective amount of the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 is administered to a mammal including human.
- 24. A method of treatment or prevention of a tumor comprising a process in which an effective amount of the carboxylic acid derivative or the pharmaceutically acceptable salt thereof according to any one of claims 3 to 9 is administered to a mammal including human.